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Stroke prevention in atrial fibrillation: comparison of recent international guidelines

Tze-Fan Chao[1,2], Milan A. Nedeljkovic[3,4], Gregory Y.H. Lip[5,6], and Tatjana S. Potpara[3,4]

[1]*Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan;*
[2]*Institute of Clinical Medicine, Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan;*
[3]*School of Medicine, University of Belgrade, dr Subotica 8, 11000 Belgrade, Serbia;*
[4]*Cardiology Clinic, Clinical Centre of Serbia, Visegradska 26, 11000 Belgrade, Serbia;*
[5]*Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool Heart & Chest Hospital, Liverpool, UK; and*
[6]*Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*

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Stroke prevention is one of the cornerstones of management in patients with atrial fibrillation (AF). As part of the ABC (Atrial fibrillation Better Care) pathway (A: Avoid stroke/Anticoagulation; B: Better symptom control; C: Cardiovascular risk and co-morbidity optimisation), stroke risk assessment and appropriate thromboprophylaxis is emphasised. Various guidelines have addressed stroke prevention. In this review, we compared the 2017 APHRS, 2018 ACCP, 2019 ACC/AHA/HRS, and 2020 ESC AF guidelines regarding the stroke/bleeding risk assessment and recommendations about the use of OAC. We also aimed to highlight some unique points for each of those guidelines. All four guidelines recommend the use of the CHA_2DS_2-VASc score for stroke risk assessment, and OAC (preferably NOACs in all NOAC-eligible patients) is recommended for AF patients with a CHA2DS2-VASc score $\geq$2 (males) or $\geq$3 (females). Guidelines also emphasize the importance of stroke risk reassessments at periodic intervals (e.g. 4–6 months) to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors.

Introduction

Atrial fibrillation (AF) is associated with an increased risk of ischaemic stroke, and stroke prevention is a cornerstone in the management of patients with AF. Oral anticoagulant therapy (OAC) with vitamin K antagonists (VKA), e.g. warfarin, reduced the risk of AF-associated stroke by 64% compared to placebo.[1] Non-VKA antagonist OAC (NOAC), including dabigatran, rivaroxaban, apixaban, and edoxaban, further reduced the risk of stroke or systemic embolic events by 19% compared to warfarin in a pooled analysis of NOACs pivotal trials.[2] The introduction of NOACs has changed the landscape of stroke prevention and led to a better clinical outcome in AF patients.[3] However, the benefits of stroke risk reduction with OAC should be carefully balanced against the risk of bleeding, and optimal stroke prevention strategy for each patient should be individualized, based on evidence and shared decision making. International cardiology societies, such as American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS), American College of Chest Physicians (ACCP), Asia Pacific Heart Rhythm Society (APHRS), and European Society of Cardiology (ESC) have published their guidelines or consensus documents to guide stroke prevention in AF in clinical practice.[4–7] Most recently, the 2020 ESC AF guidelines have been

*Corresponding author. Tel: +38 11 1361 6319, Email: tatjana.potpara@med.bg.ac.rs

Table 1 Recommended scoring schemes for stroke and bleeding risk assessments

Guidelines	Stroke risk assessment			Bleeding risk assessment
	Scoring scheme suggested for stroke risk assessment	Definitions of the stroke risk factor component	Other important statements	Scoring scheme suggested for bleeding risk assessment
2017 APHRS	CHA_2DS_2-VASc	Similar to the original definitions	—	HAS-BLED score
2018 ACCP	CHA_2DS_2-VASc	C: Recent decompensated HF, irrespective of the ejection fraction or the presence of moderate-severe LV systolic impairment on cardiac imaging, whether symptomatic or asymptomatic	—	HAS-BLED score
2019 ACC/AHA/HRS	CHA_2DS_2-VASc	Similar to the original definitions	—	No specific bleeding score was recommended
2020 ESC	CHA_2DS_2-VASc	C: Clinical HF, or objective evidence of moderate to severe LV dysfunction, or HCM V: Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque	H: Uncontrolled BP—the optimal BP target associated with the lowest risk of ischaemic stroke, death, and other cardiovascular outcomes is 120–129/<80 mmHg Age: Age-related risk is a continuum, but for reasons of simplicity and practicality, 1 point is given for age 65–74 years, and 2 points for age ≥75 years Recent data from Asia suggest that the risk of stroke may rise from age 50–55 years upwards and that a modified CHA_2DS_2-VASc score may be used in Asian patients Sc: Female sex is a stroke risk modifier rather than a risk factor	HAS-BLED score

ACC/AHA/HRS, American College of Cardiology/American Heart Association/Heart Rhythm Society; ACCP, American College of Chest Physicians; APHRS, Asia Pacific Heart Rhythm Society; BP, blood pressure; CAD, coronary artery disease; ESC, European Society of Cardiology; HF, heart failure; LV, left ventricle; PAD, peripheral arterial disease.

published containing updated information about stroke prevention in AF.

In this review, we compared the 2017 APHRS, 2018 ACCP, 2019 ACC/AHA/HRS, and 2020 ESC AF guidelines regarding the stroke/bleeding risk assessment and recommendations about the use of OAC, also highlighting some unique points in each of the guidelines.

Stroke risk assessment

The recommendations concerning stroke risk assessment are summarized in *Table 1*. All four guidelines recommend the use of CHA_2DS_2-VASc score for stroke risk assessment,[8] with some variations regarding the C (congestive heart failure) and V (vascular disease) components. In the original score derivation study,[8] 'C' refers to congestive heart failure (HF) or left ventricular (LV) dysfunction. In both ACCP and ESC guidelines, the 'C' was defined as HF with reduced (HFrEF) or preserved (HFpEF) ejection fraction, and the 2020 ESC guidelines also included hypertrophic cardiomyopathy (HCM) based on previous studies showing that the presence of HCM confers an increased stroke risk and OAC is beneficial for stroke reduction.[9,10] In addition, the ESC guidelines included angiographically significant coronary

artery disease in the 'V' component of the CHA_2DS_2-VASc score.[11]

Importantly, the 2020 ESC AF guidelines highlighted some aspects concerning the H (hypertension), A (age), and Sc (female sex) components, emphasizing that the optimal blood pressure target associated with the lowest risk of ischaemic stroke, death, and other cardiovascular outcomes among patients with AF is 120–129/<80 mmHg,[12] whereas recent data from Asia suggest that the risk of stroke may rise from age 50–55 years upwards and that a modified CHA_2DS_2-VASc score may be used in Asian patients.[13,14] Female sex is a stroke risk modifier rather than a risk factor.[15] Observational studies showed that women with no other stroke risk factors (i.e. with a CHA_2DS_2-VASc score of 1) have a low stroke risk, similar to men with a CHA_2DS_2-VASc score of 0.[16] In the presence of >1 non-sex stroke risk factor, women with AF consistently have significantly higher stroke risk than men.[15] The simplified CHA_2DS_2-VA score (without female sex) could guide the initial decision about OAC in AF patients but not considering the sex component would underestimate stroke risk in women with AF.[17]

Bleeding risk assessment

The overview of the bleeding risk assessment tools recommended in specific AF guidelines is shown in *Table 1*. The APHRS, ACCP, and ESC AF guidelines all recommend the use of the HAS-BLED score for bleeding risk assessment, while the ACC/AHA/HRS did not propose any specific bleeding risk scheme. The prior 2016 ESC AF guidelines summarized a list of non-modifiable and modifiable bleeding risk factors (including some biomarkers, e.g. the growth differentiation factor-15) and recommended correction of modifiable bleeding risk factors rather than any formal scoring.[18] However, bleeding risk assessment based solely on modifiable bleeding risk factors misses important interaction between non-modifiable and modifiable risk factors for bleeding and has been shown to be inferior to a formal bleeding risk assessment using a bleeding risk score.[19,20] Of note, most of the modifiable bleeding risk factors listed in the 2016 ESC AF Guidelines are components of the HAS-BLED score. In the new 2020 ESC AF guidelines, the HAS-BLED score is recommended to assess bleeding risk: 'For a formal risk score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥3) for early and more frequent clinical review and follow-up (Class IIa recommendation)'. Most importantly, the estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention (Class III recommendation).

Recommendations for the use of OAC and risk re-assessment

Recommendations for the use of OAC for stroke prevention based on CHA_2DS_2-VASc score and the risk re-assessment are summarized in *Table 2*. All four AF guidelines clearly favour NOACs over VKAs in all NOAC-eligible patients (i.e. those without moderate-to-severe mitral stenosis or prosthetic mechanical heart valves). The recommendations for low- and high-risk patients are generally similar in the four guidelines—OAC is not recommended for patients with a CHA_2DS_2-VASc score of 0 (males) or 1 (females), and OAC

Table 2 Recommendations of oral anticoagulants for stroke prevention based on stroke risk and the risk re-assessment

Guidelines	Tipping points and the recommendations for stroke prevention	Statements or recommendations about the risk re-assessment
2017 APHRS	OACs for patients with a score ≥1 (males) or ≥2 (females)	None
2018 ACCP	OACs should be offered for patients with a score ≥1 (males) or ≥2 (females)	Stroke risk is dynamic, and risk should be re-assessed at every patient visit
2019 ACC/AHA/HRS	Class IIb recommendation—OACs for score 1 (males) or 2 (females) Class I recommendation—OACs for score ≥2 (males) or ≥3 (females)	Re-evaluation of the need for and choice of anticoagulant therapy at periodic intervals is recommended to reassess stroke and bleeding risks
2020 ESC	Class IIa recommendation—OACs for score 1 (males) or 2 (females) Class I recommendation—OACs for score ≥2 (males) or ≥3 (females)	Class I recommendation—stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors. Class IIa recommendation—in patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made 4–6 months after the index evaluation.

ACC/AHA/HRS, American College of Cardiology/American Heart Association/Heart Rhythm Society; ACCP, American College of Chest Physicians; APHRS, Asia Pacific Heart Rhythm Society; ESC, European Society of Cardiology; OACs, oral anticoagulants.

use is recommended/indicated in those with a CHA_2DS_2-VASc score of $\geq$2 (males) or $\geq$3 (females).

A discrepancy among specific guidelines exists for recommendations about OAC use in patients with a CHA_2DS_2-VASc score of 1 (males) or 2 (females). The use of OACs for stroke prevention in these patients is recommended by the APHRS and ACCP guidelines and should be considered as per the ESC guidelines (Class IIa recommendation), whereas in the 2019 ACC/AHA/HRS guidelines the recommendation is weak (Class IIb). Actually, different risk factors would carry different weight on stroke risk,[21] and age thresholds for initiating NOACs may even differ for patients with a different single non-sex stroke risk factor, as follows: age 35 years for HF, 50 years for hypertension or diabetes, and 55 years for vascular disease.[22,23] Although no randomized control trial has specifically addressed the need for OAC in patients with a single non-sex CHA_2DS_2-VASc risk factor, an overview of subgroup analyses and observational data suggests that OAC use in such patients confers a positive net clinical benefit when balancing the reduction in stroke against the potential for harm with serious bleeding.[24-26]

An important issue pointed out in the ACCP, ACC/AHA/HRS and ESC guidelines is the importance of risk-reassessment (*Table 2*). The stroke risk in AF patients is not static as patients become older and may accumulate more comorbidities over time, which would result in an increase in the CHA_2DS_2-VASc score value.[27-29] Among patients with incident AF who initially had a CHA_2DS_2-VASc score of 0 (males) or 1 (females) and were not indicated for OAC, around 16% would have a CHA_2DS_2-VASc score $\geq$1 (males) or $\geq$2 (females) at 1-year follow-up,[30] and among such patients the use of OACs was associated with a lower composite risk of ischaemic stroke, intracranial haemorrhage, or mortality (adjusted hazard ratio, 0.530).[29] Of note, the HAS-BLED score is also dynamic,[31] and therefore, a regular bleeding risk reassessment is also recommended by the 2020 ESC AF guidelines.

What would be a reasonable time interval at which stroke risk should be re-assessed in AF patients? Based on the data from Taiwan, of patients who acquired new stroke risk factors, 80% would acquire these comorbidities after 4.2 months of AF diagnosis. The time period from the acquirement of incident comorbidities to the occurrence of ischaemic stroke was longer than 4.4 months for 90% of those patients.[29] Therefore, the ESC guidelines recommend that in patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made 4–6 months after the index evaluation (Class IIa).

Peri-cardioversion and peri-catheter ablation

The key concepts and recommendations for stroke risk management peri-cardioversion are generally similar between the 2019 ACC/AHA/HRS and 2020 ESC AF guidelines, except for some differences regarding the duration of the AF episode before cardioversion. The ESC guidelines recommend that in all patients with AF duration of >24 h undergoing cardioversion, therapeutic anticoagulation should be continued for at least 4 weeks even after successful cardioversion to sinus rhythm (beyond 4 weeks, the decision about long-term OAC treatment is determined by the presence of stroke risk factors) (class IIa), while the ACC/AHA/HRS guidelines set the AF duration threshold at $\geq$48 h. Also, in patients with a CHA_2DS_2-VASc of 0 in men or 1 in women, post-cardioversion anticoagulation for 4 weeks may be omitted for those with a definite duration of AF $\leq$24 h (ESC guidelines, Class IIb) or <48 h (ACC/AHA/HRS guidelines, Class IIb).

There are two new recommendations for stroke risk management peri-catheter ablation in the 2020 ESC AF guidelines—(i) in AF patients with stroke risk factors not taking OAC before ablation, it is recommended that pre-procedural management of stroke risk includes initiation of anticoagulation and, preferably, therapeutic OAC for at least 3 weeks before ablation (Class I), or alternatively, the use of transoesophageal echocardiography to exclude LA thrombus before ablation (Class IIa); and (ii) For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without OAC interruption is recommended (Class I). While not interrupting NOACs peri-catheter ablation is favoured in all AF guidelines, the 2020 ESC AF guidelines clearly defined the term 'uninterrupted'. Although this term is frequently used in clinical practice for the description of regimens where one or two NOAC doses are omitted before ablation, NOAC administration before ablation was truly uninterrupted in the randomized controlled trials comparing uninterrupted NOACs vs. warfarin. Therefore, the 2020 ESC AF guidelines stated that there is no reason to recommend omitting one or two NOAC doses before ablation, as the administration of the first dose the evening after ablation or the next morning (if this corresponds to the timing of the next dose according to the patient's previous OAC regimen) appeared to be safe.

Specific conditions with challenging treatment decision-making

There are several specific conditions such as advanced chronic kidney disease (CKD), advanced liver disease/liver cirrhosis, and atrial high rate episodes (AHRE) where high-quality evidence is lacking and treatment decision-making for the prevention of AF-related stroke may be challenging. The specific guideline recommendations/statements referring to these scenarios are summarized in *Table 3*.

Patients with AF and stage IV (CrCl 15–29 mL/min) CKD or end-stage renal disease [ESRD; creatine clearance (CrCl) <15 mL/min or on dialysis] are at increased risk for both stroke and bleeding. There is no high-quality randomized trial-based evidence informing the use of VKAs or NOACs compared to non-OAC in this population (the RENAL-AF trial (NCT02942407) of apixaban vs. warfarin in patients with AF on haemodialysis was stopped prematurely and was inconclusive regarding relative stroke and bleeding rates). Therefore, most of the recommendations regarding the use of VKAs or NOACs in these patients (where provided) are based on pharmacokinetic data or observational

Table 3 Recommendations/statements of stroke prevention in special scenarios and left atrial appendage occlusion

Guidelines	Advanced CKD	Advanced liver disease/ liver cirrhosis	AHREs	LAAO
2017 APHRS	• In patients with ESRD or dialysis, NOACs are contraindicated. Although VKA with good-quality anticoagulation control (TTR > 70%) might be useful, the data are lacking	—	—	• Interventional percutaneous LAA closure with the WATCHMAN device may be considered in patients with non-valvular AF who have high risk of stroke, but major contraindications to OAC therapy • Surgical excision of the LAA may be considered in patients undergoing concomitant cardiac surgery
2018 ACCP	• In stage IV (CrCl 15-30 mL/min) CKD, suggesting using VKAs and selected NOACs [rivaroxaban 15 mg QD, apixaban 2.5 mg bid, edoxaban 30 mg QD, and (in USA only) dabigatran 75 mg bid] with caution, based on pharmacokinetic data • In end-stage renal disease (CrCl < 15 mL/min or dialysis-dependent), suggesting using well-managed VKA with TTR >65–70%	• Patients with liver function abnormalities were generally excluded from the randomized trials, and especially where there is abnormal clotting tests, such patients may be at higher risk of bleeding on VKA, possibly less so on NOACs; in cirrhotic patients, ischaemic stroke reduction may outweigh bleeding risk.	• In patients with AF, prescription of OACs could be considered as a result of an individualized clinical assessment taking into account overall AHRE burden (in the range of hours rather than minutes) and specifically, the presence of AHRE >24 h, individual stroke risk (using CHA_2DS_2-VASc), predicted risk benefit of OACs and informed patient preferences (Ungraded consensus-based statement)	• In patients with AF at high risk of ischaemic stroke who have absolute contraindications for OAC, suggesting using LAA occlusion (Weak recommendation, low quality evidence) • In AF patients at risk of ischaemic stroke undergoing cardiac surgery, we suggest surgical exclusion of the LAA for stroke prevention, but the need for long-term OAC is unchanged (Weak recommendation, low quality evidence)
2019 ACC/AHA/ HRS	• Class IIb - For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women and who have ESRD (CKD; CrCl <15mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation	-	• Prospective clinical trials of prophylactic anticoagulation based on device-detected AF are under way but have not been completed • Although increased duration of AHREs is associated with increased stroke risk, the threshold duration of AHREs that warrants anticoagulation is unclear • Current approaches factor in the duration of device-detected AF and the patient's stroke risk profile, bleeding risk, an preferences to determine whether to initiate long-term anticoagulation	• Class IIb - Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation
2020 ESC	• In patients with CrCl 15-29 mL/min, RCT-derived data on the effect of VKA or NOACs are lacking	• Patients with hepatic dysfunction were generally excluded from the RCTs • Despite the paucity of data, observational	• The use of OAC may be considered in selected patients with longer durations of AHRE/subclinical AF (≥24 h) and an estimated high	• Class IIb - LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment

(continued)

Table 3 Continued

Guidelines	Advanced CKD	Advanced liver disease/ liver cirrhosis	AHREs	LAAO
	• The evidence for the benefits of OAC in patients with end-stage kidney disease with CrCl $\leq$ 15 mL/min or on dialysis is even more limited, and to some extent controversial	studies did not raise concerns regarding the use of NOACs in advanced hepatic disease • NOACs are contraindicated in patients within Child-Turcotte-Pugh C hepatic dysfunction, and rivaroxaban is not recommended for patients in the Child-Turcotte-Pugh B or C category	individual risk of stroke, accounting for the anticipated net clinical benefit and informed patient's preferences	• Class IIb - Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery

ACC/AHA/HRS, American College of Cardiology/American Heart Association/Heart Rhythm Society; ACCP, American College of Chest Physicians; AF, atrial fibrillation; AHRE, atrial high rate episode; APHRS, Asia Pacific Heart Rhythm Society; CKD, chronic kidney disease; CrCl, creatinine clearance; ESC, European Society of Cardiology; ESRD, end-stage renal disease; INR, international normalized ratio; LAAO, left atrial appendage occlusion; NOACs, non-vitamin K antagonist oral anticoagulants; OACs, oral anticoagulants; RCTs, randomized controlled trials; TTR, time in therapeutic range; VKA, vitamin K antagonist.

studies. Generally, if a VKA is prescribed, a high time in therapeutic range (TTR > 70%) is crucial for its optimal effect. For stage IV (CrCl 15–29 mL/min) CKD, the ACCP guidelines suggest the use of VKAs or selected NOACs [rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily, edoxaban 30 mg once daily or (in USA only) dabigatran 75 mg bid] with caution, based on pharmacokinetic data. For ESRD patients (CrCl < 15 mL/min or on dialysis) having a CHA_2DS_2-VASc score $\geq$2 (males) or $\geq$3 (females), the ACC/AHA/HRS guidelines stated that it might be reasonable to prescribe warfarin [international normalized ratio (INR) 2.0–3.0] or apixaban for oral anticoagulation (Class IIb). Differently, there was no formal recommendation for ESRD patients in the ESC guidelines which only mentioned that the evidence for the benefit of OAC in patients with end-stage kidney disease with CrCl <15 mL/min or on dialysis is limited, and to some extent controversial. Further high-quality randomized trials are necessary to inform us how to manage these patients.

Data about the use of OACs among AF patients with advanced liver cirrhosis are very limited,[32] and such patients were not included in pivotal NOACs trials on stroke prevention in AF. There are no formal recommendations in the four guidelines for this scenario, with some statements provided in the ACCP and 2020 ESC AF guidelines (*Table 3*). Importantly, all NOACs are contraindicated in patients within Child-Turcotte-Pugh C hepatic dysfunction, and rivaroxaban is not recommended for patients in the Child-Turcotte-Pugh B or C category.

The use of NOACs for stroke prevention in patients with AHRE is tested in two ongoing trials, the ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; NCT 01938248) and NOAH (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; NCT 02618577) trial. Previously, the ASSERT trial showed that the presence of AHRE (atrial rate >190 b.p.m. for more than 6 min) was associated with a higher risk of ischaemic stroke or systemic embolism (hazard ratio, 2.49).[33] Further analysis of the ASSERT trial demonstrated that the increased risk of ischaemic stroke or systemic embolism was only observed for patients with the longest episode of AHRE >24 h.[34] Therefore, the 2020 ESC AF guidelines suggest that OACs may be considered in selected patients with longer duration of AHRE/subclinical AF ($\geq$24 h) and an estimated high individual risk of stroke, accounting for the anticipated net clinical benefit and informed patient's preference.

Left atrial appendage occlusion

There are no high-quality, large-scale randomized trials comparing the efficacy and safety of NOACs and left atrial appendage occlusion (LAAO) for stroke prevention in AF, and in all four AF guidelines, LAAO is recommended as a second-line treatment for stroke prevention. For example, the 2020 ESC AF guidelines recommend that LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (Class IIb). Also, surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery (Class IIb).

Conclusions

All four guidelines suggest the use of the CHA_2DS_2-VASc score for stroke risk assessment, and OAC (preferably NOACs in all NOAC-eligible patients) is recommended for AF patients with a CHA_2DS_2-VASc score $\geq$2 (males) or $\geq$3 (females). Three of the four guidelines (except for ACC/AHA/HRS guidelines) suggest that OAC should be considered for patients with a CHA_2DS_2-VASc score of 1 (males) or 2 (females). Guidelines also emphasize the importance of risk reassessments at periodic intervals (e.g. 4–6 months for stroke risk by ESC guidelines) to inform treatment decisions (e.g. initiation of OAC in patients no

longer at low risk of stroke) and address potentially modifiable bleeding risk factors. Further studies are necessary to guide clinical practice in some special/difficult scenarios.

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